

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Currently amended) ~~An isolated~~ Isolated JAK2 protein (Janus kinase 2) characterized in that it ~~comprises a mutation on amino acid 617, more particularly comprising the V617F mutation, hereinafter called "JAK2 V617F variant" whose~~ and having the sequence is shown in SEQ ID NO 1, ~~or a similar sequence in other mammals.~~
2. (Currently amended) ~~An isolated nucleotide~~ Nucleotide sequence encoding the JAK2 ~~V617F variant~~ protein according to claim 1, ~~in particular sequence SEQ ID NO 2 having the t/g mutation at position 1849 starting at the ATG marking the start of transcription.~~
3. (Currently amended) ~~A cloning~~ Cloning and/or viral expression vector, either plasmid or in naked DNA form, characterized in that it comprises the nucleotide sequence according to claim 2 under the control of ~~an efficient~~ a promoter in mammalian cells.
4. (Currently amended) ~~A mammalian~~ Mammalian cell expressing the ~~recombinant isolated JAK2 protein V617F variant~~ according to claim 1.
5. (Withdrawn) Non-human transgenic animal expressing recombinant JAK2 V617F according to claim 1.
6. (Withdrawn) Non-human transgenic animal according to claim 5, characterized in that it is a mouse or rat having integrated into its genome at least the sequence encoding JAK2 V617F by homologous recombination or directed recombination.
7. (Withdrawn) Non-human transgenic animal according to claim 5, characterized in that it is homozygous JAK2 V617F / JAK V617F or heterozygous JAK2 V617F / JAK2, said animals reproducing Vaquez polyglobulia and/or myeloproliferative disorders induced by JAK2 V617F.

8. (Currently amended) A probe or primer ~~Probes or primers~~ comprising 10 to 30 consecutive nucleotides of sequence SEQ ID NO 3 or 4 and comprising the mutated nucleotide t<sup>1849</sup>.

9. (Currently amended) A probe or primer ~~Probes or primers~~ according to claim 8 chosen from among sequences SEQ ID NO 5 to 11 and 15 to 28.

10. (Withdrawn) *Ex vivo* or *in vitro* method to determine the presence or absence of the G1849T variant of the JAK2 gene in a sample from a patient suffering from PV or likely to develop PV or any other myeloproliferative disorder, in particular erythrocytoses, hyperleukocytoses, thrombocytoses and myelofibroses, method comprising:

- a) obtaining a nucleic acid sample from the patient,
  - b) detecting the presence or absence of the G1849T variant of the JAK2 gene in said nucleic acid sample,
- characterized in that the presence of the G1849T variant is an indication of PV or of any other myeloproliferative disorder.

11. (Withdrawn) Method according to claim 10, characterized in that it comprises a hybridisation step with at least one probe or primer comprising 10 to 30 consecutive nucleotides of sequence SEQ ID NO 3 or 4 and comprising the mutated nucleotide t<sup>1849</sup>.

12. (Withdrawn) Method according to claim 10, characterized in that it comprises an amplification step by PCR reaction with at least one pair of primers comprising 10 to 30 consecutive nucleotides of sequence SEQ ID NO 3 or 4 and comprising the mutated nucleotide t<sup>1849</sup>.

13. (Withdrawn) Method according to claim 10, characterized in that it is performed on the mRNA of an individual and comprises a RT-PCR reaction.

14. (Withdrawn) Method according to claim 10, characterized in that it comprises an amplification step by means of said primers, followed by a hybridisation step with at least one probe, preferably two probes which hybridise under conditions of high stringency to the sequences corresponding to the region of the G1849T mutation, and detection of the signal

produced by the markers of said probes, the probes and primers comprising 10 to 30 consecutive nucleotides of sequence SEQ ID NO 3 or 4 and comprising the mutated nucleotide t<sup>1849</sup>.

15. (Withdrawn) Method according to claim 10 comprising the detection of the presence or absence of the G1849T variant of the JAK2 gene in said nucleic acid sample by means of one or more SNPs (Single Nucleotide Polymorphism) specific to the G1849T mutation of the JAK2 gene, in particular sequences SEQ ID NO 17 and 18, 23 and 24 or 27 and 28.

16. (Withdrawn) *Ex vivo* or *in vitro* method to detect the presence or absence of the JAK2 V617F variant in a sample from a patient suffering from or likely to develop PV or any other myeloproliferative disorder, method comprising:

- a) obtaining a sample from the patient,
- b) detecting the presence or absence of the JAK2 V617F variant,

characterized in that the presence of said variant is an indication of PV or of any other myeloproliferative disorder.

17. (Withdrawn) Method according to claim 16 comprising the contacting of the sample with an antibody specific to the V617F variant of the JAK2 protein, preferably an antibody capable of making the distinction between the V617F variant and the non-mutated JAK2 protein.

18. (Withdrawn) Method according to claim 17, characterized in that the antibodies are monoclonal or polyclonal antibodies, single chain or double chain, chimeric or humanised antibodies or binding fragments to the antigen F(ab')<sub>2</sub> and F(v).

19. (Withdrawn) Method according to claim 18, characterized in that it is an ELISA test.

20. (Withdrawn) Method according to claim 10, characterized in that it is conducted for the sub-population of patients showing a hematocrit level of over 51%.

21. (Withdrawn) Method according to claim 10, characterized in that it is conducted for the sub-population of patients showing a platelet count of more than 450,000.
22. (Withdrawn) Monoclonal antibody specifically recognizing the JAK2 V617F variant.
23. (Withdrawn) Hybdridoma producing an antibody according to claim 22.
24. (Currently amended) A kit [[Kit]] for detecting the JAK2 V617F variant in a tumor, wherein the kit comprises ~~tumour comprising~~ one or more primers or probes such as defined in claim 8 for the specific detection of the presence or absence of the G1849T mutation in the JAK2 gene.
25. (Currently amended) A kit [[Kit]] for determining whether a patient is suffering from ~~Vaquez polyglobulia or from any other~~ a myeloproliferative disorder involving the JAK2 V617F variant, ~~in particular erythrocytoses, hyperleukocytoses, thrombocytoses and myelofibroses,~~ comprising one or more probes or primers such as defined in claim 8 for the specific detection of the presence or absence of the G1849T mutation in the JAK2 gene.
26. (Currently amended) A kit [[Kit]] according to claim 24 also containing at least one element chosen from among a heat resistant polymerase for PCR amplification, one or more solutions for amplification and/or ~~the~~ hybridisation step and any reagent allowing the detection of the JAK2 V617F variant ~~marker~~.
27. (Withdrawn) Kit to determine whether a patient is suffering from Vaquez polyglobulia or any other myeloproliferative disorder involving the JAK2 V617F variant, containing an antibody according to claim 22.
28. (Cancelled).
29. (Currently amended) An isolated siRNA capable of reducing by more than 50% the expression of the JAK2 V617F variant according to claim 1, ~~siRNA according to claim 28,~~ characterized in that it has 19 to 25 nucleotides, ~~preferably 19 nucleotides~~ in length, the sequence of a first strand being identical and the sequence of a second strand being

complementary to sequence SEQ ID NO 3, SEQ ID NO 4 or SEQ ID NO 11 comprising the mutated t<sup>1849</sup> nucleotide.

30. (Currently amended) An siRNA according to claim 29 [[28]], characterized in that it induces a reduction of more than 80% ~~or 95%~~ of the expression of JAK2 V617F and in that it only induces a reduction of less than 25% ~~or 5%~~ of the expression of wild-type JAK2.

31. (Currently amended) An siRNA according to claim 29 [[28]], characterized in that it is chosen from the group consisting of:

- UGGAGUAUGUUUCUGUGGA (SEQ ID NO 29)
- GGAGUAUGUUUCUGUGGAG (SEQ ID NO 30) and
- GAGUAUGUUUCUGUGGAGA (SEQ ID NO 31).

32. (Withdrawn) Method with which to determine the specific inhibition of JAK2 V617F by one or more compounds comprising the steps consisting of:

- a) contacting one or more compounds with the JAK2 V617F protein according to claim 1, a membrane fraction containing JAK2 V617F, or a cell expressing JAK2 V617F according to claim 4 under suitable conditions for fixing and/or inhibition, and
- b) detecting the specific fixing and/or inhibition of JAK2 V617F.

33. (Withdrawn) Screening method comprising a succession of tests according to claim 32 of several molecules and a selection step to select molecules having an IC50 for JAK2 V617F that is less than 1  $\mu$ M, preferably 100 nM.

34. (Withdrawn) Method according to claim 33 also comprising a negative selection of the molecules having an IC50 for JAK2 of less than 5  $\mu$ M or 1  $\mu$ M.

35. (Withdrawn) *In vitro* screening method according to claim 32, wherein the inhibition of JAK2 V617F phosphorylation is determined by immunoprecipitation.

36. (Withdrawn) *In vivo* screening method according to claim 32 on primary CD34+ JAK2 V617F progenitor cells which are capable of differentiating without erythropoietin (Epo), or on cell lines which have become factor independent through the introduction of the JAK2 V617F variant.

37. (Withdrawn) *In vivo* screening method according to claim 32 using a mammalian cell expressing the recombinant JAK2 V617F variant protein of SEQ ID NO 1, or a similar sequence in other mammals.

38. (Withdrawn) Method for identifying candidate medicinal products comprising the steps of:

- a) administering compounds to a non-human transgenic animal expressing JAK2 V617F such as defined in any of claims 5 to 7, said animal reproducing Vaquez polyglobulia and/or having a myeloproliferative disorder associated with the presence of JAK2 V617F,
- b) determining the effect of the compound and selecting the candidate medicinal products which are seen to reduce or block the proliferation and spontaneous differentiation of the erythroblasts of Vaquez polyglobulia, or to reduce cell proliferation associated with the presence of JAK2 V617F.

39. (Withdrawn) A method of producing a medicinal product in accordance with siRNAs according to claim 29 [[28]].

40. (Withdrawn) A method according to claim 39 wherein the medicinal product prepared is intended for the treatment of malignant hemopathies, in particular myeloproliferative disorders including Vaquez polyglobulia, essential thrombocythemia, myeloid splenomegaly or primitive myelofibrosis.

41. (Withdrawn) A method according to claim 39 wherein the medicinal product prepared is intended for the treatment of myeloproliferative disorders associated with the JAK2 V617F mutation, and other malignant hemopathies and solid tumours such as carcinomas, melanomas and neuroblastomas, which express JAK2 V617F.

42. (Currently amended) A composition ~~Composition~~ comprising a siRNA according to claim 29 [[28]] and a pharmaceutically acceptable vehicle.